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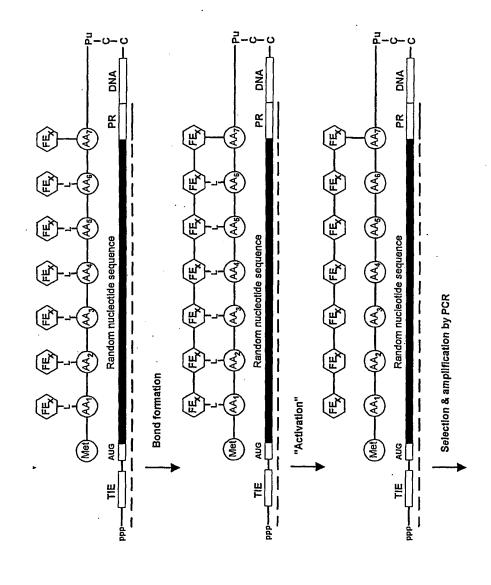
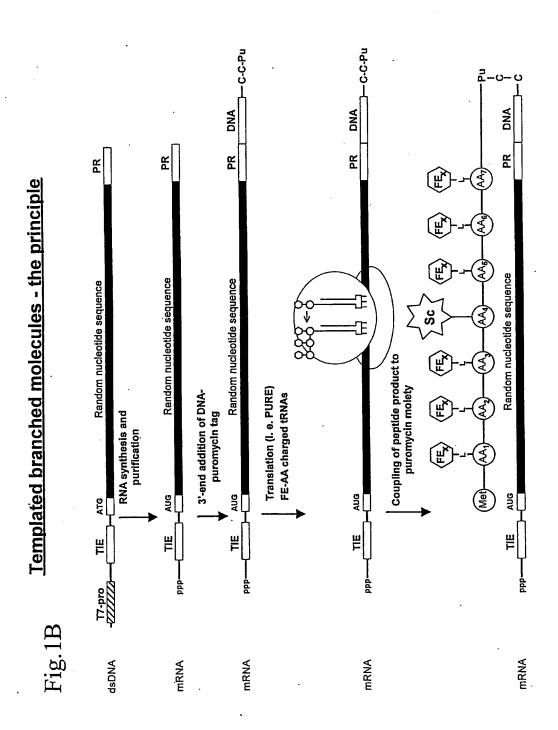
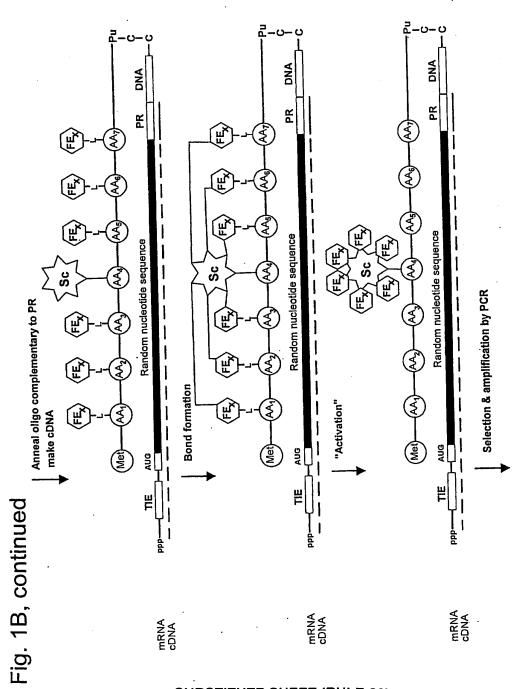


Fig. 1A, continued

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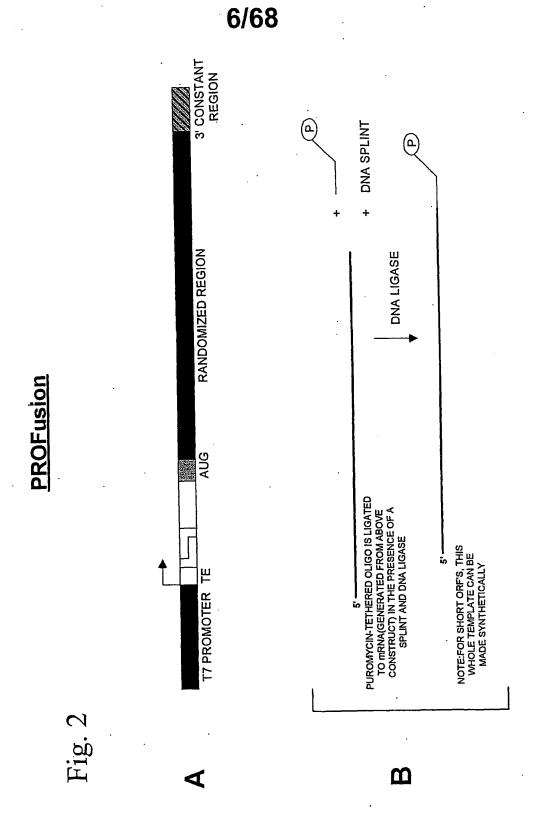
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Fig. 1C

Display of Functional Entities on a Peptide Backbone



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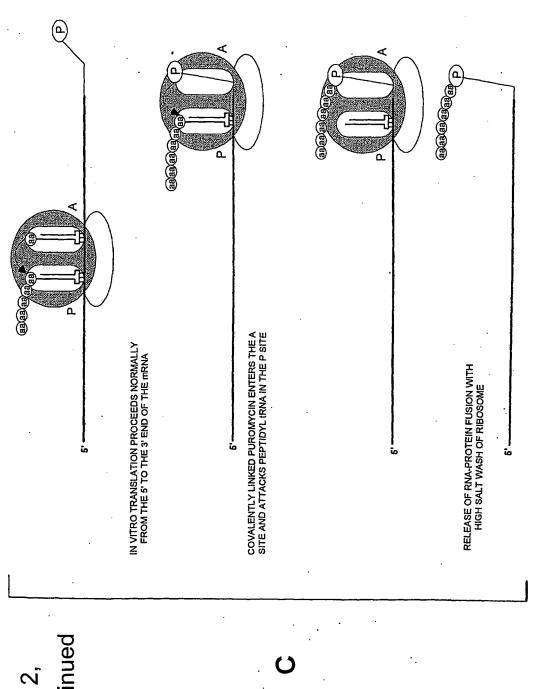


Fig. 2, continue

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Fig. 4A Example of a first building block

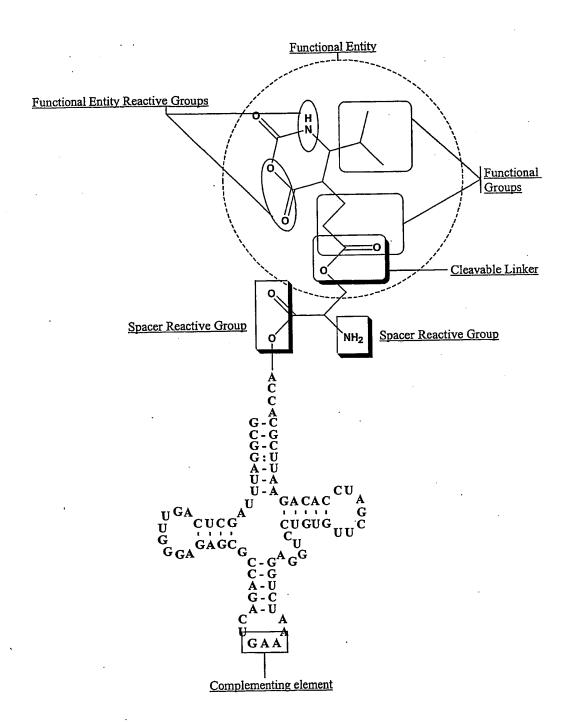
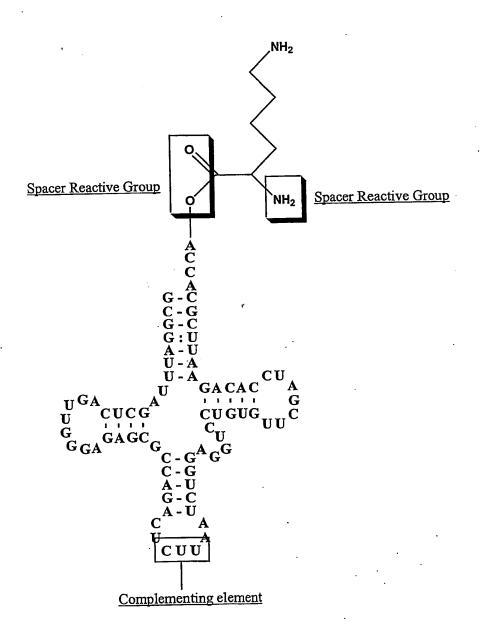


Fig. 4B

Example of a second building block



Examples of tRNAs charged with FE-AA units

Fig. 4C

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Fig. 4C, continued

16)

Fig. 5A

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Enzymatic charging of tRNAs catalysed by amino acid tRNA synthetases

Fig. 5B Chemical aminoacylation of tRNAs

Fig. 6

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Bond formation between functional entities and activation of the templated molecule

Fig. 7

alpha-helix display of functional entities

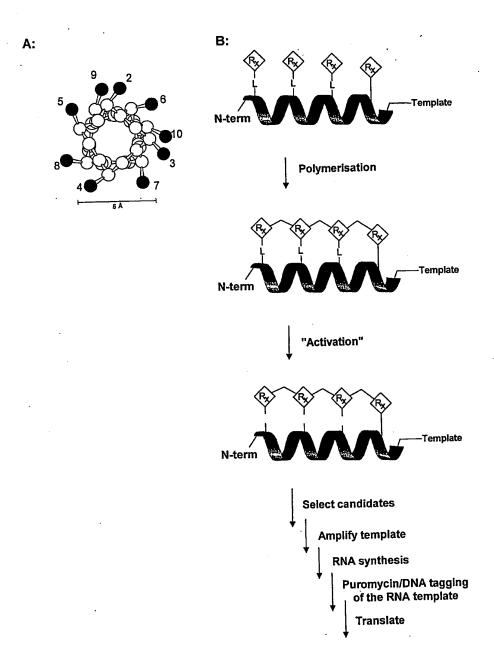
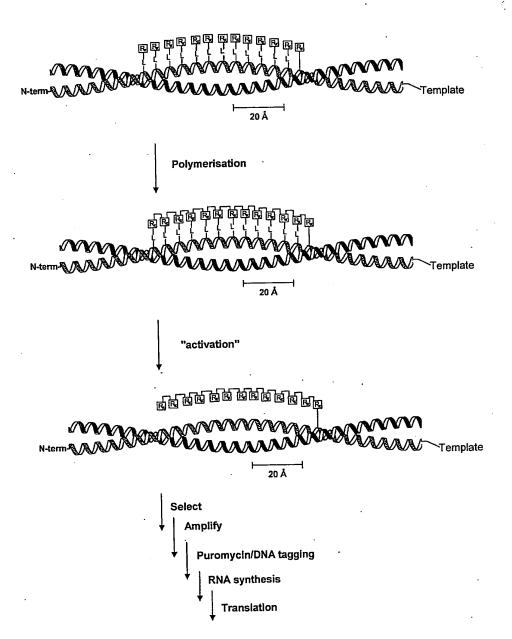


Fig. 8

Coiled-coil display of functional entities



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Fig. 9

. Display of functional entities by a collagen-like triple helix structure

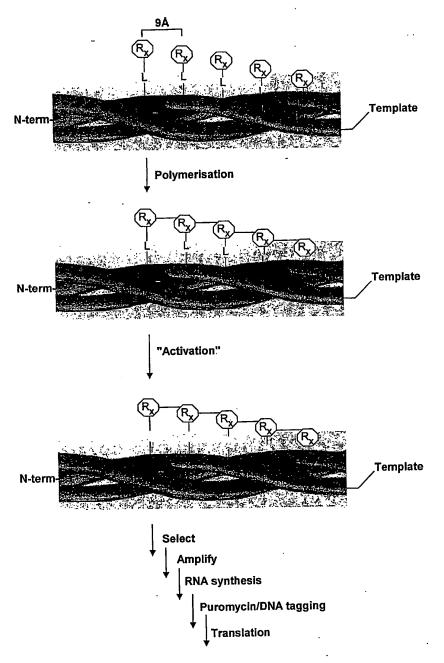


Fig. 10

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Cleavable linkers and protection groups, cleaving agents and cleavage products.

A. Base (nucleophilic) cleavage.

B. Photocleavage

$$R \longrightarrow NO_2$$
 $O \longrightarrow R$
 $R \longrightarrow CHO + CO_2 + HOF$
 $Ar \longrightarrow SO_2 \longrightarrow R'$
 $Ar \longrightarrow SO_3 \longrightarrow R'$
 $R \longrightarrow R'$

Fig. 10, continued

C. Acid cleavage

D. Catalytic cleavage.

$$R \xrightarrow{H_2} R \xrightarrow{H_2} + HOR$$

Fig. 10, continued

E. Enzymatic cleavage.

F. Cleavage by temperature increase.

$$R \xrightarrow{+} N - R' \qquad A \qquad + \qquad N - R'$$

G. Miscellaneous

Fig. 11
Polymerization by reaction between neighboring reactive groups.

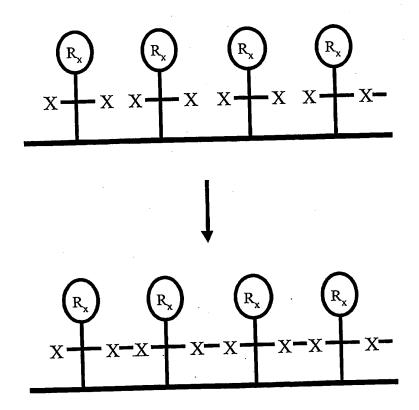


Fig. 11, continued

Ex. 1. Coumarin-based polymerization

Fig 12. Polymerization between neighboring non-identical reactive groups.

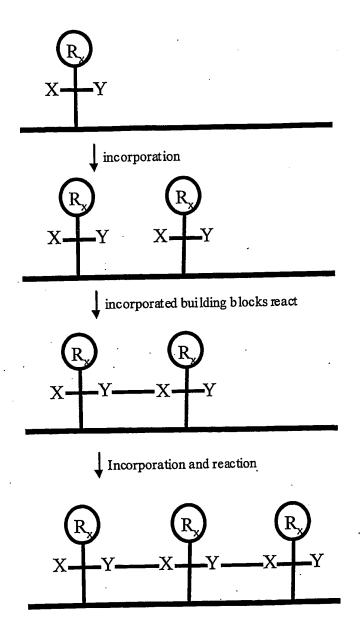


Fig. 13. Cluster for mation in the absence of directional polymerization.

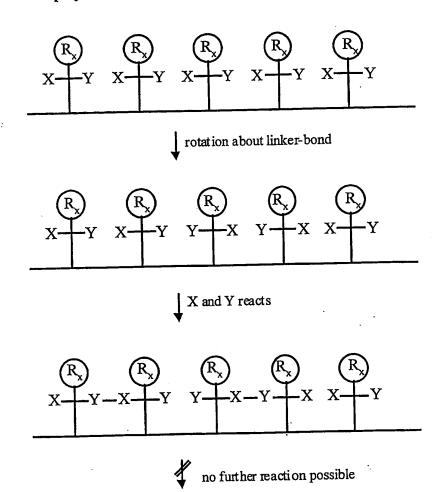


Fig 14. Zipping-polymerization and simultaneous activation.

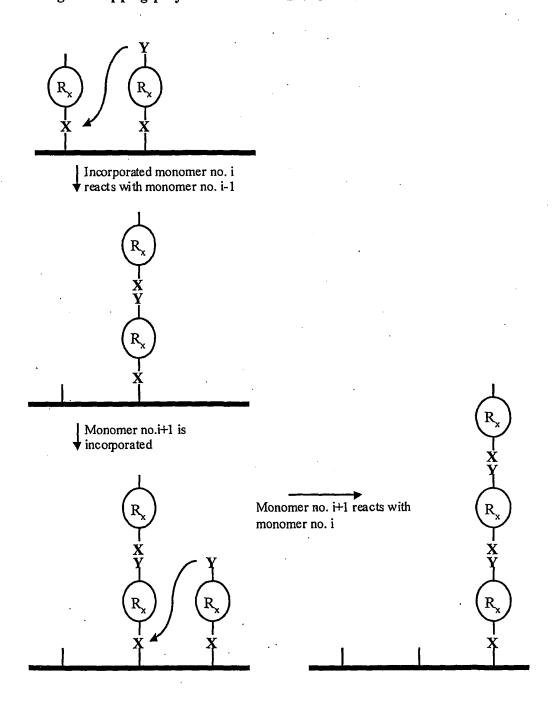


Fig. 14, continued 31/68

Example 1. Polymerization and activation (thioesters)

A.

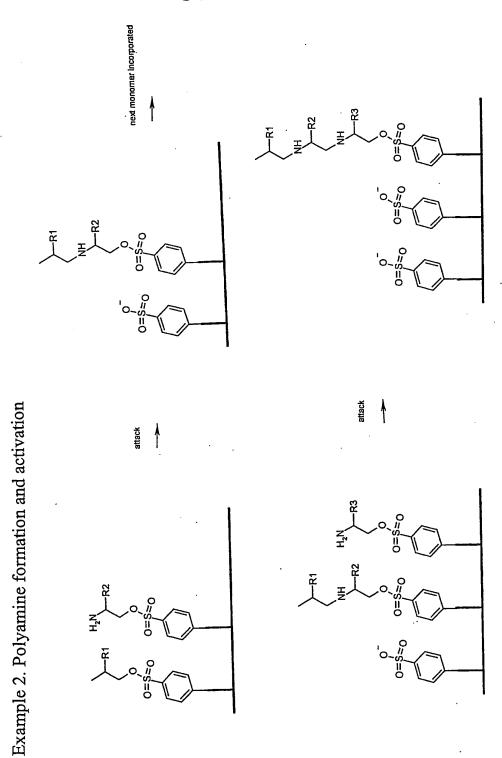
$$R1$$
 $O \Rightarrow R2$
 $O \Rightarrow R1$
 $O \Rightarrow R2$
 $O \Rightarrow R1$
 $O \Rightarrow R2$
 $O \Rightarrow R1$
 $O \Rightarrow R2$
 $O \Rightarrow R2$
 $O \Rightarrow R3$
 $O \Rightarrow R3$
 $O \Rightarrow R1$
 $O \Rightarrow R1$
 $O \Rightarrow R1$
 $O \Rightarrow R2$
 $O \Rightarrow R3$
 $O \Rightarrow R1$
 $O \Rightarrow R2$
 $O \Rightarrow R3$
 $O \Rightarrow R3$
 $O \Rightarrow R1$
 $O \Rightarrow R2$
 $O \Rightarrow R3$
 $O \Rightarrow R4$
 $O \Rightarrow R$

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Fig. 14, continued

Fig. 14, continued

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Fig. 15 "Fill-in" polymerization (symmetric XX monomers).

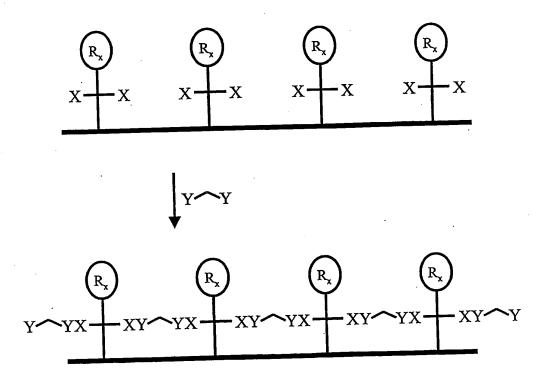


Fig. 15, continued

Example 1. Poly-imine formation by fill-in polymerization

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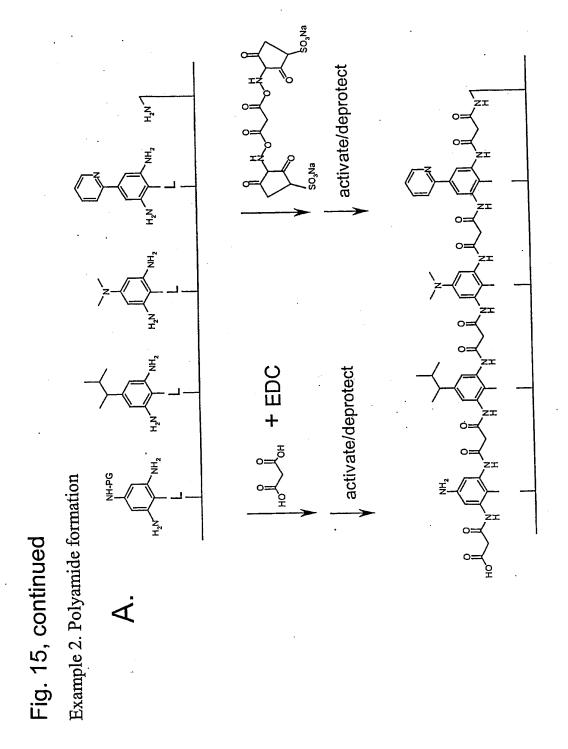
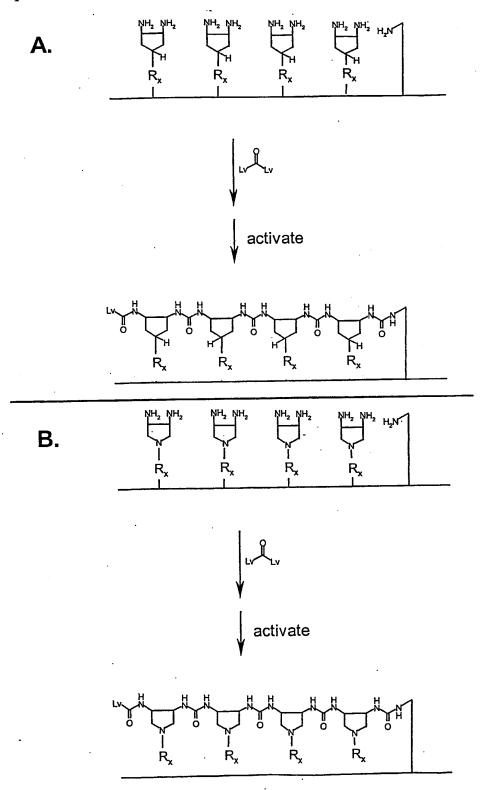


Fig. 15, continued

Example 3. Polyurea formation

Fig. 15, continued 39/68

Example 4. Chiral and achiral polyamide backbone formation



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Fig. 15, continued

Example 5. Polyphosphodiester formation

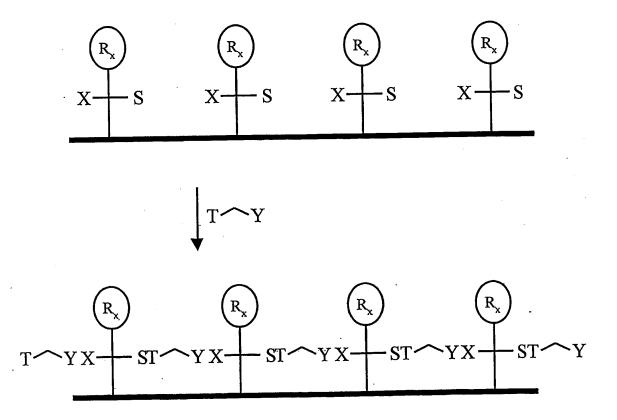
Fig. 15, continued

Example 6. Polyphosphodiester formation with one reactive group in each monomer building

Fig. 15, continued

Example 7. Pericyclic, "fill-in" polymerization

Fig. 16. "Fill-in" polymerization (asymmetric XS monomers).

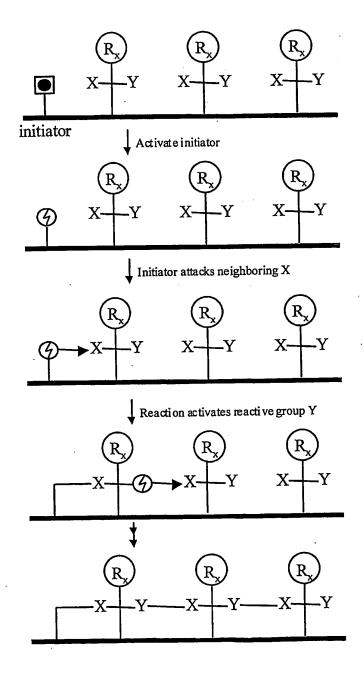


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Example 1. Fill-in polymerization by ketone-hydrazide reaction and by modified Staudinger ligation activation Fig. 16, continued

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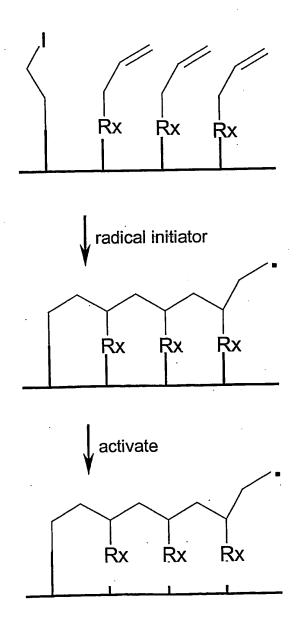
Fig. 17
"Zipping" polymerization



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Fig. 17, continued

Example 1. Radical polymerization



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Fig. 17, continued. Example 2. Cationic polymerization

Fig. 18. Zipping polymerization by ring opening.

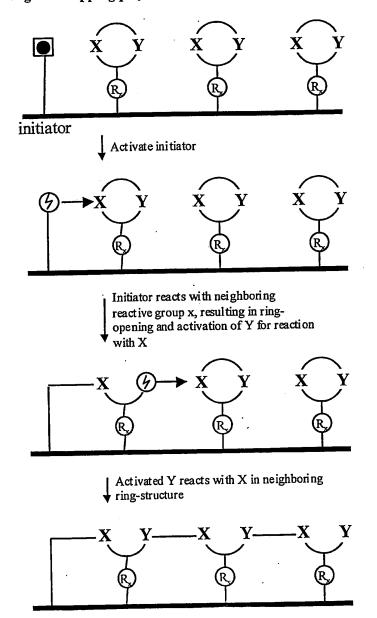


Fig. 18, continued. Example 1.

"Zipping" polymerization of N-thiocarboxyanhydrides, to form \(\beta \)-peptides.

Fig. 18, continued. Example 2. "Zipping" polymerization of 2,2-diphenylthiazinanone units to form β-peptides.

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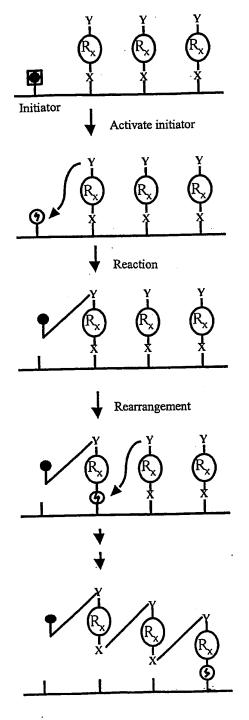
Fig. 18, continued. Example 3. Polyether formation by ring-opening polymerization.

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Fig. 19

Zipping-polymerization and activation by rearrangement.

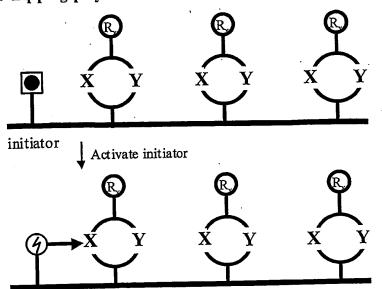


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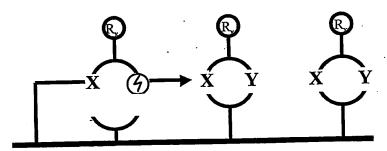
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Fig. 20. Zipping-polymerization and activation by ring opening.



Initiator and X reacts, resulting in ring-opening and activation of Y. The functional entity is simultaneously released from complementing element



Polymerisation and linker cleavage migrates along the spacer backbone

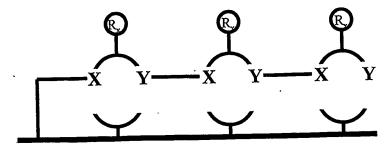
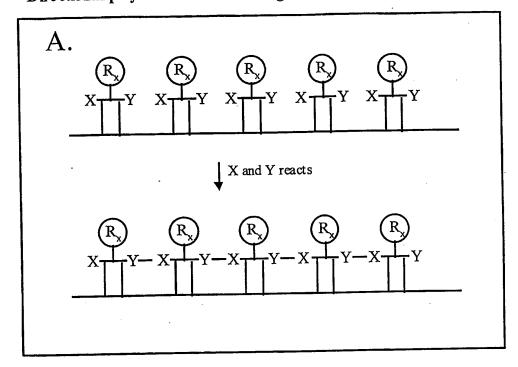


Fig. 21.

Directional polymer formation using fixed functional units.



$$B.$$

$$O_2N$$

$$O_1$$

$$O_2N$$

$$O_1$$

$$O_2$$

$$O_3$$

$$O_4$$

$$O_4$$

$$O_4$$

$$O_4$$

$$O_4$$

$$O_4$$

$$O_4$$

$$O_7$$

$$O_8$$

Fig. 22. Templated polymers.

- alpha-, beta-, gamma-, and omega-peptides
- mono-, di- and tri-substituted peptides
- L- and D-form peptides
- cyclohexane- and cyclopentane-backbone modified beta-peptides
- vinylogous polypeptides
- glycopolypeptides
- polyamides
- vinylogous sulfonamide peptide
- Polysulfonamide
- conjugated peptide (i.e., having prosthetic groups)
- Polyesters
- Polysaccharides
- Polycarbamates
- Polycarbonates
- Polyureas
- poly-peptidylphosphonates
- Azatides
- peptoids (oligo N-substituted glycines)
- Polyethers
- ethoxyformacetal oligomers
- poly-thioethers
- polyethylene glycols (PEG)
- Polyethylenes
- Polydisulfides
- polyarylene sulfides
- Polynucleotides
- PNAs
- LNAs
- Morpholinos
- oligo pyrrolinone
- polyoximes
- Polyimines
- Polyethyleneimine
- Polyacetates
- Polystyrenes
- Polyacetylene
- Polyvinyl
- Lipids
- Phospholipids
- Glycolipids
- polycycles (aliphatic)
- polycycles (aromatic)
- polyheterocycles
- Proteoglycan
- Polysiloxanes
- Polyisocyanides
- Polyisocyanates
- Polymethacrylates

Fig. 23. Precursors - examples.

- N-carboxyanhydrides (NCA)
- N-thiocarboxyanhydrides (NTA)
- Amines
- Carboxylic acids
- Ketones
- Aldehydes
- Hydroxyls
- Thiols
- Esters
- Thioesters
- conjugated system of double bonds
- Alkyl halides
- Hydrazines
- N-hydroxysuccinimide esters
- Epoxides
- Haloacetyls
- UDP-activated saccharides
- Sulfides
- Cyanates
- Carbonylimidazole
- Thiazinanones
- Phosphines
- Hydroxylamines
- Sulfonates
- Activated nucleotides
- Vinylchloride
- Alkenes, quinones

Fig. 24. Functional groups - examples.

- Hydroxyls
- Primary, secondary, tertiary amines
- Carboxylic acids
- Phosphates, phosphonates
- Sulfonates, sulfonamides
- Amides
- Carbamates
- Carbonates
- Ureas
- Alkanes, Alkenes, Alkynes
- Anhydrides
- Ketones
- Aldehydes
- Nitatrates, nitrites
- Imines
- Phenyl and other aromatic groups
- Pyridines, pyrimidines, purines, indole, imidazole, and heterocyclic bases
- Heterocycles
- polycycles
- Flavins
- Halides
- Metals
- Chelates
- Mechanism based inhibitors
- Small molecule catalysts
- Dextrins, saccharides
- Fluorescein, Rhodamine and other fluorophores
- Polyketides, peptides, various polymers
- Enzymes and ribozymes and other biological catalysts
- Functional groups for post-polymerization/post activation coupling of functional
- groups
- Drugs, e.g., taxol moiety, acyclovir moiety, "natural products"
- Supramolecular structures, e.g. nanoclusters
- Lipids
- Oligonucleotides, oligonucleotide analogs (e.g., PNA, LNA, morpholinos)

Fig. 25. Polymers and the functional entities required to make them.

A.

	Functional Entity		ļ	General	Specific
Polymer	(reactive groups)	Linking molecule	Catalyst/reagent	Figure	Figure
polycyclic	+				
compound	di-coumarin		light	Fig. 11	Fig. 11, ex.
001119-00110	or oddinario				
				Fig. 12,	
polyester	alcohol, carboxylic acid		carbodiimide	Fig. 21	
polyester	hydroxyl, thioester			Fig. 14	-
	At	acrhanddimidazala		Fig. 15	Fig 15, ex. 3
polyurea	di-amine	carbonyldiimidazole	 	171g. 13	rig 15, ex. 5
	+			Fig. 12,	
polyacetate	halogen, carboxylic acid		base	Fig. 21	
· · · · · · · · · · · · · · · · · · ·			EDC or other	Fig. 12,	
polyacetate	alcohol, carboxylic acid		carbodiimide	Fig. 21	
				<u> </u>	<u> </u>
				Fig. 12,	}
polycarbamate	alcohol, isocyanate			Fig. 21	
polycarbonate	diol	carbonyldiimidazole		Fig. 15	
	 			Fig. 12,	ļ
	secondary amine, α-		}		}
peptoid	haloacelyl			Fig. 21 Fig. 12,	
	primary amine, α-	}	alladolina saost	Fig. 12, Fig. 21	}
	haloacetyl		alkylating agent	FIG. 21	
			glycogen	Fig. 12,	
glycogen	UDP-glucose		synthetase	Fig. 21	
<u> </u>	UDP-activated		polysaccharide	Fig. 12,	
polysaccharide	saccharides		synthetases	Fig. 21	
, , , , , , , , , , , , , , , , , , ,	glucosyl				
	sulphide/sulfoxide	}	}]	
	activation system (Kahne	}	}	Fig. 12,	
polysaccharide	glucosylation)		Kahne conditions	Fig. 21	
	amine, N-			Fig. 12,	
polyamide	hydroxysuccinimide ester	ł	}	Fig. 21	
polyanilue	Tryuruxyauconniniue eater	 		Fig. 12,	
polyamide	amine, carboxylic acid	1	carbodìimide	Fig. 21	}.
polyamide	jamine, carboxylic acid	ļ	Carpoullitude	119.21	

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Fig. 25, continued
Polymers and the functional entities required to make them.

B

	Functional Entity (reactive groups)	Linking molecule	Catalyst/reagent	General Figure	Specific Figure
Polymer			carbodiimide	Fig. 15	Fig. 15, ex. 2
30170.11.00	di-amine	di-carboxylic acid	carbodiimide	Fig. 15	Fig. 15, ex. 2
polyamide	di-carboxylic acid .	di-amine	carbodimide	rig. 10	
polyamide	amine, carboxylic acid	amine, carboxylic acid	carbodiimide	Fig. 16	
α-polypeptide	carboxyanhydride (5- membered ring)			Fig. 18	
β-polypeptide	carboxyanhydride (6 membered ring)			Fig. 18	Fig. 18, ex.1
γ-polypeptide	carboxyanhydride (7- membered ring)			Fig. 18	
α-polypeptide	2,2-diphenylthiazinanone (5-membered ring)			Fig. 18	
β-polypeptide	2,2-diphenylthiazinanone (6-membered ring) 2,2-diphenylthiazinanone			Fig. 18	Fig. 18, ex.2
γ-polypeptide	(7-membered ring)			Fig. 18	
α-polypeptide	amine, thioester			Fig. 14	
β-polypeptide	amine, thioester			Fig. 14	Fig. 14, ex.1
γ-polypeptide	amine, thioester	1		Fig. 14	
ω-polypeptide	amine, thioester			Fig. 14	<u> </u>
polysulfonamide	amine, sulfonic acid		carbodiimide	Fig. 12, Fig. 21	
polyphosphonate	di-alcohol	activated phosphonate		Fig. 15	
polyphosphonate	di-alcohol	activated alkylphosphine	oxidating reagent e.g. tert- butylhydroperoxid e	Fig. 15	
polyphosphate	di-alcohol .	diaminoalkoxy- phosphine	oxidating reagent e.g. tertbutyl- hydroperoxide	Fig. 15	
			<u> </u>	<u> </u>	
polyphosphodiester		diaminophosphine	oxidant (ButOOH		Fig. 15, ex. 5
polyphosphodiester	diaminophosphine	diol	oxidant (ButOOH) Fig. 15	Fig. 15, ex. 6

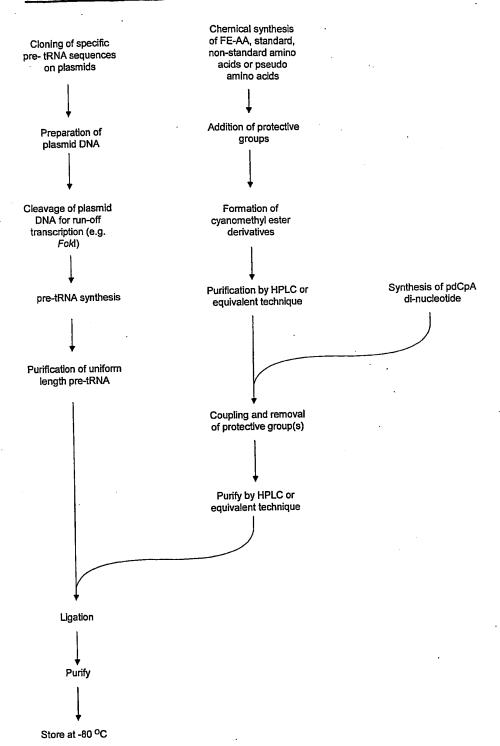
Fig. 25, continued Polymers and the functional entities required to make them.

 \mathbf{C}

Functional Entity	Linking molecule	Catalyst/reagent	General Figure	Specific Figure
11. 04.04.1			Fig. 15	
diamine				
enoxide			Fig. 18	Fig. 18, ex. 3
Operation				
thioepoxide			Fig. 18	
thiol, thiol		oxidant	Fig. 11	
aldehyde, hydroxylamine		·	Fig. 12, Fig. 21	
-ldshude amino			Fig. 12,	
	 		Fig. 15	Fig. 15, ex. 1
aluellyue, arriine				
	2-		Fig. 12,	
methylimidazolides			119.21	
amine, alkyl sulfonate			Fig. 14	Fig. 14, ex.2
alkene			Fig. 17	Fig. 17, ex. 1
			Fig. 17	Fig. 17, ex.2
alkerie				
di-diene	di-alkene (benzoquinone)		Fig. 15	Fig. 15, ex. 7
vinvichloride Unit	-		Fig. 17	
VIITYIGIIOITGG GITTE				
styrene-unit		radical initiator, AIBN	Fig. 17	<u>.</u>
othylono unit	-		Fig. 17	Fig. 17, ex.
	aldehyde, hydroxylamine aldehyde, amine aldehyde, amine nucleoside-5'-phosphoro- methylimidazolides amine, alkyl sulfonate alkene alkene di-diene vinylchloride unit	diamine diisocyanate epoxide thioepoxide thioi, thioi aldehyde, hydroxylamine aldehyde, amine aldehyde, amine nucleoside-5'-phosphoro-2- methylimidazolides amine, alkyl sulfonate alkene di-alkene di-diene vinylchloride unit styrene-unit	diamine diisocyanate epoxide thioepoxide thiol, thiol oxidant aldehyde, hydroxylamine aldehyde, amine aldehyde, amine nucleoside-5'-phosphoro-2- methylimidazolides amine, alkyl sulfonate alkene di-diene di-diene vinylchloride unit styrene-unit diisocyanate oxidant oxidant oxidant di-alkene aldehyde, amine aldehyde, amine aldehyde, amine di-dene radical initiator, AIBN	diamine disocyanate Fig. 15 epoxide Fig. 18 thioepoxide Fig. 18 thiol, thiol oxidant Fig. 11 aldehyde, hydroxylamine Fig. 21 aldehyde, amine aldehyde, amine Fig. 15 nucleoside-5'-phosphoro-2-methylimidazolides Fig. 12, Fig. 21 amine, alkyl sulfonate Fig. 15 alkene Fig. 17 di-alkene (benzoquinone) Fig. 17 styrene-unit Fig. 17

Fig. 26

Protocol for chemical charging of specific tRNAs

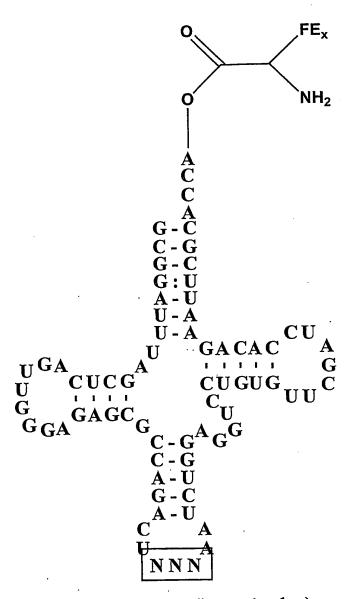


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Fig. 27A

An example of a general structure for a set of building blocks.



Variable sequence (i.e. anticodon)

Fig. 27B

Examples of anticodon sequences and their corresponding functional entities

Fig. 28

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Bond formation and linker cleavage

EDC/NHS (pH 8.0)

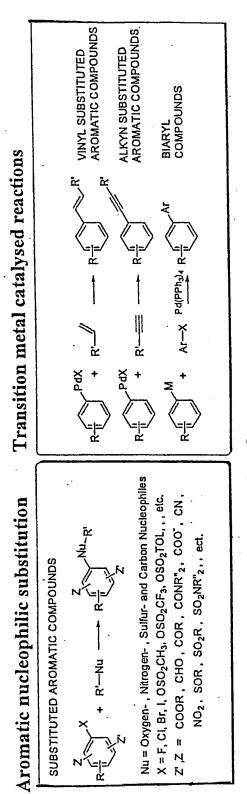
Photocleavage of linkers (and protective groups)

Pairs of reactive groups X, Y and the resulting bond XY.

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	R— S THIOAMIDES HN—R" THIOAMIDES	+ R"—NH ₂ —— R—	S-R' HN-R" S THIOAMIDES	HN-R"	R"—X + N OXIMES	R"-SO ₂ CI + R'N'-R' - R"SO ₂ -N' SULFONAMIDES	$R'-X$ + $R-\stackrel{Z'}{\leftarrow}$ \longrightarrow $R-\stackrel{Z'}{\leftarrow}$ DI- AND TRI-	$R' = \begin{pmatrix} Z' \\ + R + \begin{pmatrix} Z' \\ + Z \end{pmatrix} \end{pmatrix}$ $R = \begin{pmatrix} Z' \\ + R + \end{pmatrix} \end{pmatrix} \end{pmatrix} \end{pmatrix} \end{pmatrix} \right)$ $ \begin{pmatrix} 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1 & 1$	z,z = cooR, CHO, COR, CONR"2, COO',	NO2, SOR, SO2R, SO2NR"2, CN, ed.
Nucleophilic substitution reaction	R-X + R'-O R-O-R' ETHERS	R-X + R'-S' R-S-R' THIOETHERS R-X + R'-NH ₂ R-N-R' sec- AMINES	. + R*N-R' R*N-R' + R + R	+ R'-O' HO OR' B-HYDROXY ETHERS	O + R'-S' HO SR' B-HYDROXY THIOETHERS	O + R'-NH ₂ HO NHR' B-HYDROXY AMINES	R RHN OR B-AMINO THERS	$\begin{bmatrix} A & A & A & A & A & A & A & A & A & A $	R-Q + R"-NH, R-A AMIDES	S-R' HN-R"

Fig. 29, continued



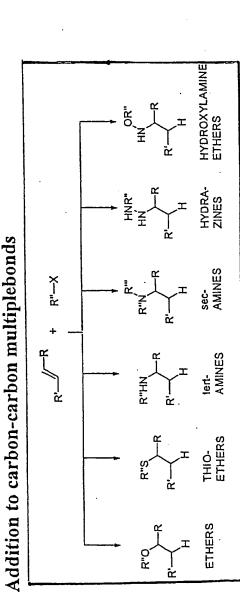


Fig. 29, continued

٠, ,	
z' + ==-z" z' z' z'' ALKENES	Z = H, Alkyl, Ar, Z" = Z', Alkyl, Ar, Z' = COOR, CHO, COR, CONR" ₂ , CN, NO ₂ , SOR, SO ₂ R, SO ₂ NR" ₂ , ect.
$\begin{pmatrix} z \\ + \\ + \\ R'' \end{pmatrix} = \begin{pmatrix} R'' \\ - \\ Z \end{pmatrix} \begin{pmatrix} R'' \\ - \\ - \\ Z \end{pmatrix} \begin{pmatrix} R'' \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\ - \\$	Z = H, Alkyl, Z', Ar Z" = COOR, CHO, COR, CONR" ₂ , CN, NO ₂ , SOR, SO ₂ R, SO ₂ NR" ₂ ,, ect, Z' = Z' R = R', = R', = Z

Cycloaddition to multiple bounds

Fig. 29, continued

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Substituted Alkenes Substituted Alkenes Z = COOR, CHO, COR, SOR, SO₂R, CN, NO₂, ect. Z_1 , Z_2 = COOR, CHO, COR, CONR"2, CN, NO2, SOR, SO₂NR"2, ect. $R^n = H$, Alkyl, Aryl R" = R", H, Alkyl, COR, R = R', H, Alkyl, Ar, B-Hydroxy Aldehydes p-Hydroxy Ketones Substituted Amines Substituted Amines Addition to carbon-hetero multiple bonds NaBH₃CN R-NH2

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